Controversial issues in Gleason and International Society of Urological Pathology (ISUP) prostate cancer grading: proposed recommendations for international implementation

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Abstract: The Gleason Grading system has been used for over 50 years to prognosticate and guide the treatment for patients with prostate cancer. At consensus conferences in 2005 and 2014 under the guidance of the International Society of Urological Pathology (ISUP), the system has undergone major modifications to reflect modern diagnostic and therapeutic practices. The 2014 consensus conference yielded recommendations regarding cribriform, mucinous, glomeruloid and intraductal patterns, the most significant of which was the removal of any cribriform pattern from Gleason grade 3. Furthermore, a Gleason score grouping system was endorsed which consisted of five grades where Gleason score 6 (3+3) was classified as grade 1 which better reflected the mostly indolent behaviour of these tumours. Another issue discussed at the meeting and subsequently endorsed was that in Gleason score 7 cases, the percentage pattern 4 should be recorded. This is especially important in situations where modern active surveillance protocols expand to include men with low volume pattern 4. While major progress was made at the conference, several issues were either not resolved or not discussed at all. Most of these items relate to details of assignment of Gleason score and ISUP grade in specific specimen types and grading scenarios. This detailed review looks at the 2014 ISUP conference results and subsequent literature from an international perspective and proposes several recommendations. The specific issues addressed are percentage pattern 4 in Gleason score 7 tumours, percentage patterns 4 and 5 or 4/5 in Gleason score 8-10 disease, minor (5%) high grade patterns when either 2 or 3 patterns are present, level of reporting (core, specimen, case), dealing with grade diversity among site (highest and composite scores) and reporting scores in radical prostatectomy specimens with multifocal disease. It is recognised that for many of these issues, a strong evidence base does not exist, and further research studies are required. The proposed recommendations mostly reflect consolidated expert opinion and they are classified as established if there was prior agreement by consensus and provisional if there was no previous agreement or if the item was not discussed at prior consensus conferences. For some items there are reporting options that reflect the local requirements and diverse practice models of the international urological pathology community. The proposed recommendations provide a framework for discussion at future consensus meetings.

DOI: https://doi.org/10.1016/j.pathol.2019.05.001

Originally published at:
Srigley, John R; Delahunt, Brett; Samaratunga, Hemamali; Billis, Athanase; Cheng, Liang; Clouston, David; Evans, Andrew; Furusato, Bungo; Kench, James; Leite, Katia; MacLennan, Gregory; Moch, Holger; Pan, Chin-Chen; Rioux-Leclercq, Nathalie; Ro, Jae; Shanks, Jonathan; Shen, Steven; Tsuzuki, Toyonori; Varma, Murali; Wheeler, Thomas; Yaxley, John; Egevad, Lars (2019). Controversial issues in Gleason and International Society of Urological Pathology (ISUP) prostate cancer grading: proposed recommendations for international implementation. Pathology, 51(5):463-473.
DOI: https://doi.org/10.1016/j.pathol.2019.05.001

Pathology (August 2019) **51(5)**, pp. 463–473

REVIEW

Controversial issues in Gleason and International Society of Urological Pathology (ISUP) prostate cancer grading: proposed recommendations for international implementation

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Summary

The Gleason Grading system has been used for over 50 years to prognosticate and guide the treatment for patients with prostate cancer. At consensus conferences in 2005 and 2014 under the guidance of the International Society of Urological Pathology (ISUP), the system has undergone major modifications to reflect modern diagnostic and therapeutic practices. The 2014 consensus conference yielded recommendations regarding cribriform, mucinous, glomeruloid and intraductal patterns, the most significant of which was the removal of any cribriform pattern from Gleason grade 3. Furthermore, a Gleason score grouping system was endorsed which consisted of five grades where Gleason score 6 (3+3) was classified as grade 1 which better reflected the mostly indolent behaviour of these tumours. Another issue discussed at the meeting and subsequently endorsed was that in Gleason score 7 cases, the percentage pattern 4 should be recorded. This is especially important in situations where modern active surveillance protocols expand to include men with low volume pattern 4. While major progress was made at the conference, several issues were either not resolved or not discussed at all. Most of these items relate to details of assignment of Gleason score and ISUP grade in specific specimen types and grading scenarios. This detailed review looks at the 2014 ISUP conference results and

Print ISSN 0031-3025/Online ISSN 1465-3931
DOI: https://doi.org/10.1016/j.pathol.2019.05.001

subsequent literature from an international perspective and proposes several recommendations. The specific issues addressed are percentage pattern 4 in Gleason score 7 tumours, percentage patterns 4 and 5 or 4/5 in Gleason score 8–10 disease, minor (≤5%) high grade patterns when either 2 or 3 patterns are present, level of reporting (core, specimen, case), dealing with grade diversity among site (highest and composite scores) and reporting scores in radical prostatectomy specimens with multifocal disease. It is recognised that for many of these issues, a strong evidence base does not exist, and further research studies are required. The proposed recommendations mostly reflect consolidated expert opinion and they are classified as established if there was prior agreement by consensus and provisional if there was no previous agreement or if the item was not discussed at prior consensus conferences. For some items there are reporting options that reflect the local requirements and diverse practice models of the international urological pathology community. The proposed recommendations provide a framework for discussion at future consensus meetings.

Key words: Prostate adenocarcinoma; grading; ISUP grade; Gleason; International Society of Urological Pathology.

Received 28 May, revised 30 May, accepted 31 May 2019
Available online 3 July 2019

INTRODUCTION

In November 2014, the International Society of Urological Pathology (ISUP) hosted a consensus conference on Gleason grading which was attended by 82 invited experts in prostate cancer from 19 countries.[1] The purpose of the meeting was to update the grading system for prostate cancer which had last been formally modified by the ISUP in 2005.[2] Certain grading issues had not been resolved at the earlier consensus meeting and in the ensuing decade new research data has been published. In addition, there was pressure from epidemiologists and public health experts to contain the 'overdiagnosis and over-treatment' of prostate cancer. Furthermore, active surveillance is now being embraced by many in the urology and oncology communities as a preferred approach in patients with low grade and low volume cancer.[3] In view of this, guidelines were needed to clarify grading criteria for low grade prostate cancer, in order to more accurately identify patients suitable for enrolment into active surveillance programs.

At the 2014 meeting many issues were addressed, including refinements in the assignment of patterns that comprise the Gleason grades, the most important of which was that no cribriform pattern was to be classified as Gleason grade 3. A novel Gleason diagram was developed incorporating the changes for which there was consensus (Fig. 1). A major part of the meeting was devoted to the endorsement of a five level prognostic grading system based upon the criteria of the 2005 ISUP modification of Gleason scores and grades. Numerous studies have, in the past, argued for the establishment of a grading system for prostate cancer based upon the grouping of Gleason criteria.[4] Importantly, the classification adopted at the 2014 ISUP conference, while unique in itself, did include a number of recommendations dating back to the groupings proposed by Gleason in 1977.[5] Following the consensus conference the prognostic significance of the grading system accepted by the delegates has been validated in separate studies.[6–9] The name of the grouping system was controversial from the outset. The 2016 World Health Organization (WHO) blue book avoided recommending a formal nomenclature and used the descriptive term 'grade group'.[10] While this term was subsequently used in the American Joint Committee on Cancer (AJCC) TNM8 Manual, the 'ISUP grade' is the official term endorsed by the ISUP Council in March 2015.[4,11] This naming was in keeping with prior grading systems such as for urothelial carcinoma[12] and renal cell carcinoma,[13] and the renal tumour classification system[14] resulting from ISUP sponsored consensus conferences. ISUP grade is also the recommended terminology in the International Collaboration of Cancer Reporting (ICCR) datasets for reporting of prostate cancer, which outline minimum requirements for the reporting of cancer specimens.[15–18] Aside from the naming matter, there are several emerging and controversial issues that were not fully addressed in the published report of the 2014 conference.[1] Some of these matters were discussed, at least in part, at the consensus conference and others have been raised subsequently. Many issues relate to the specific rules of assigning Gleason scores, ISUP grades and derivative measurements (Table 1).

It is acknowledged that in a recent publication, selected practical issues for implementing conference recommendations are discussed by a sub-group of the organising committee.[19] Our current review presents a detailed discussion of controversial issues emanating from the 2014 conference and subsequent literature and proposes reporting guidelines for everyday practice. Additionally, areas for future research are highlighted.

Emerging issues that will not be dealt with here include the prognostic significance of sub-patterns of Gleason grades 4 and 5, and specifically whether the presence of intraductal carcinoma and/or invasive cribriform carcinoma should affect assignment of the Gleason score and ISUP grade. These topics will be addressed at a future ISUP consensus conference, along with the potential of using image analysis algorithms based on machine learning as decision support tools in the grading of prostate cancer.

There is recognition of the diversity of urological pathology practice globally, based on local clinical expectations, practice settings and available resources. The content of this manuscript has been reviewed by a diverse group of international experts in prostatic pathology and the recommendations are constructed in a manner to allow some flexibility in their international implementation.

PERCENTAGE (%) PATTERN 4 IN GLEASON SCORE 7 CASES

The value of subdividing Gleason score 7 cancers into two categories with primary pattern 3 (GS 3+4=7) or 4 (GS 4+3=7) is well established[20,21] and indeed modern nomograms and risk calculators incorporate this split.[22,23] The ISUP grading system formally recognises this subdivision with Gleason 3+4=7 being ISUP grade 2 and 4+3=7 ISUP grade 3. The amount of Gleason pattern 4 in a score 7 case is a continuous variable and there are some compelling reasons why a finer stratification is important.[24–26] The clinicians in

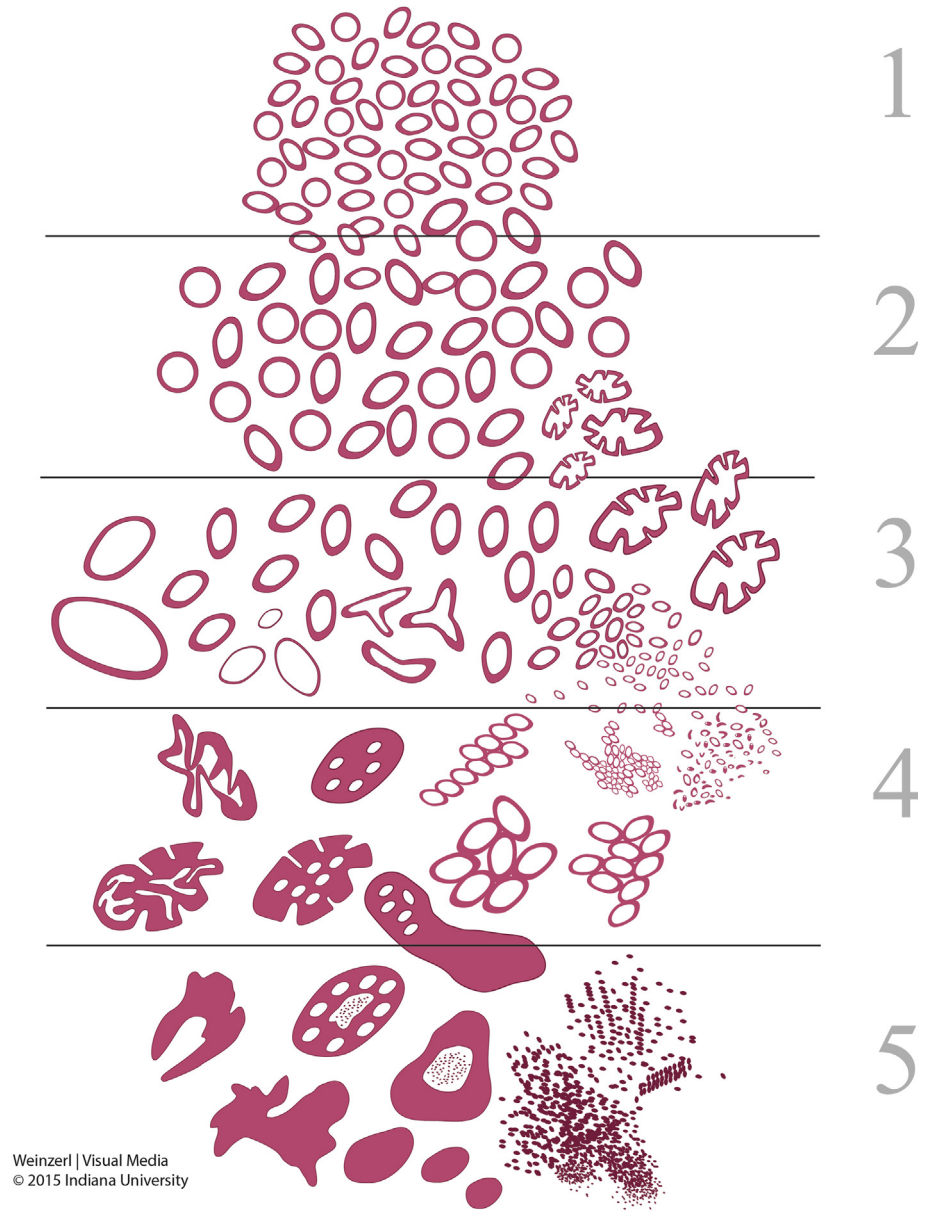

Fig. 1 Novel Gleason diagram from the 2014 ISUP consensus conference. Note absence of any cribriform pattern in grade 3.

attendance at the 2014 consensus conference agreed that reporting the % pattern 4 present would be helpful for patient management. While the issue was not voted on at the consensus conference, post-conference polling of the attendees showed widespread support for including this measurement in pathology reports. The 2016 WHO blue book also recommends that % pattern 4 be recorded in GS 7 cases.[10] Furthermore, the % pattern 4 is required for GS 7 (3+4) in the College of American Pathologists checklists and is recommended by the ICCR prostate datasets.[15–18,27]

Table 1 Controversial issues in Gleason grading

Issues in Gleason grading
• Percentage (%) pattern 4 in Gleason score 7
• Percentage (%) patterns 4 and 5 or 4/5 in Gleason score 8–10
• Minor high-grade or low-grade patterns when two Gleason grades are present (NB, TUR/SP, RP)
• Minor (≤5%) and non-minor (6–33%) high-grade patterns (Gleason 5) when three grades are present (NB, TUR/SP, RP)
• Level of reporting Gleason score and derivatives (core, specimen, case)
• Dealing with grade diversity among cores/specimens
• Dealing with grade diversity in multifocal tumours in RP (dominant nodule issue)

NB, needle biopsy; RP, radical prostatectomy; TUR/SP, transurethral resection/simple prostatectomy.

The measurement of % pattern 4 has greatest value in the low range of GS 3+4=7. Most patients being considered for active surveillance have GS 3+3=6; however, there are some protocols which permit consideration of patients with GS 3+4=7 when there is a small amount of pattern 4.[28] Recently, in a guideline developed by Cancer Care Ontario and endorsed by the American Society of Clinical Oncology it was recommended that some patients with GS 3+4=7 and ≤10% pattern 4 be considered for active surveillance if other factors, including serum prostate specific antigen (PSA) and biopsy extent measurements are favourable.[3]

In borderline cases between GS 3+4=7 and GS 4+3=7, the recording of the % pattern 4 provides greater transparency regarding the subjectivity of the assignment. For instance, a GS 3+4=7 tumour with 45–50% pattern 4 differs little from a GS 4+3=7 tumour with 50–55% pattern 4. Similarly, at the high end of the range, it is useful to know if the prostate cancer is GS 4+3=7 (ISUP grade 3) with 90% pattern 4 and 10% pattern 3 which is close on the scale to a tumour with >95% pattern 4 and ≤5% pattern 3. The latter would be graded as GS 4+4=8 (ISUP grade 4) using a rule established at the 2005 ISUP consensus meeting.[2]

In Gleason score 7 cases showing grade heterogeneity among sites, the % pattern 4, if reported at case level (see later discussion) can provide important information; for instance, if there are multiple sites involved, with a mixture of GS 3+3=6, 3+4=7 and 4+3=7 tumour, many urologists and oncologists, and especially those in North America, would take GS 4+3=7 as the definitive grade for treatment purposes.[29] There may only be a single site with GS 4+3=7 tumour in a core with minimal cancer involvement, say 10%. In such a case, the overall % pattern 4 could be less than 5%. In contrast if all sites show GS 4+3=7, then the overall % pattern 4 would range from 50–95%. The % pattern 4 measurement allows urologists and oncologists to better understand the actual amount of high grade tumour present in the biopsy.

There are several questions that arise relating to the reporting of % Gleason pattern 4. Should this measurement be reported at core, specimen or case level (see later section)? Should the amount of pattern 4 be measured as a percentage by linear extent or surface area, or as an actual length in millimeters? Should the cellular density be considered and how does one deal with intimately admixed patterns 3 and 4? Is the % pattern 4 measurement reproducible? At present there are no satisfactory data to provide evidenced based answers to these questions. Future research studies need to be designed and executed to advance the field.

It is proposed that at the very least the % pattern 4 measurement should be reported at case level with core and specimen level reporting being optional depending on local practice patterns and clinical expectations. Since % linear involvement and/or linear millimeters are recommended as general tumour extent measures, the % pattern 4 can be derived using similar techniques. Future research and consensus activities will address that importance of identifying and measuring sub-patterns of Gleason grade 4.

Regarding the stratification of % pattern 4, there are many potential methods. Since ≤5% is used in the definition of a 'minor high-grade pattern', this category should be captured in the measurement system.[1] Additionally, since ≤10% is incorporated into some active surveillance protocols, this fraction should also be captured.[3] It is suggested that the scale be as follows: ≤5%, 6–10%, 11–20% and subsequent deciles up to 91–100%. A further issue relates to whether there should be a certain amount of tumour present in a core to accurately assign % pattern 4. It can be difficult to decide whether a very small focus of cancer in a needle core is GS 3+4=7 or 4+3=7, let alone to measure % pattern 4.[30] It has been suggested that because of lack of reproducibility, the assignment of % pattern 4 should be considered optional in small foci of Gleason score 7 adenocarcinoma.[30] While arbitrary, a small focus may be defined as 3 mm or less.

Finally, % pattern 4 has to be interpreted in the context of tumour extent, as 90% pattern 4 in a 4 mm focus would not have the same prognostic significance as 90% pattern 4 in a 20 mm focus. In such cases, the minute size of the malignant focus and the associated uncertainty concerning the assigned Gleason score may be addressed in a supporting comment.

PERCENTAGE (%) PATTERNS 4 AND 5 OR 4/5 IN GLEASON SCORE 8–10 CASES

McNeal *et al.* first proposed the reporting of % 4/5 in 1990 and later showed that this parameter was an independent predictor of recurrence after radical prostatectomy.[24,26,31] These authors also reported that nodal metastases occurred, with only one exception, in patients with ≥3.2 mL of Gleason 4/5 in their radical prostatectomy specimens.[24] In a watchful waiting cohort with long term follow-up, in which tumour was diagnosed at time of transurethral resection, the % 4/5 was found to be an independent predictor of adverse survival.[32] Sauter *et al.* in a recent study showed the value of quantitative Gleason grading by recording the fraction of Gleason patterns 3, 4 and 5 in a large series of radical prostatectomy specimens.[25] The authors emphasised that Gleason grade represents a continuum and that the quantitative approach provides prognostic information beyond that of ISUP grades.

In Gleason score 7 cases, the % patterns 4/5 equates with % pattern 4 and is discussed in an earlier section. The reporting of % pattern 4/5 in GS 7 cases could cause confusion for some clinicians who may wonder why pattern 5 is mentioned at all; however, it is easy to explain that % pattern 4/5 = % pattern 4 and/or pattern 5.

Is there a value in reporting the % 4/5 in cases with scores 8–10? In biopsy cases, there is large variation in the amounts of high-grade cancer that may be present. This can present problems when there is grade diversity among cores and when grading is based on the core with the highest Gleason score. A case could be classified as Gleason score 8 (ISUP Grade 4) when one site shows GS 4+4=8 while all other positive cores show mixtures of 3+3=6, 3+4=7 and 4+3=7. If the core with GS 4+4=8 is only minimally involved by cancer, the overall % 4/5 may be less than 5%. This differs from the case where all involved sites show GS 4+4=8 and the % 4/5 is 100%. One would expect the behaviour of these latter tumours to be different from that of the former tumour and yet both are classified as GS 4+4=8 for treatment purposes if the highest Gleason score is used. The % 4/5 metric also permits stratification of the uncommon GS 3+5=8 and 5+3=8 cases which can range from 3+5=8 with less than 5% pattern 5 to 5+3=8 with 94% pattern 5. If there is 95% pattern 5, the tumour would be graded as 5+5=10 using the rules established at the 2005 ISUP consensus conference.[2]

In biopsy cases where there are three grades present and the highest grade is the third most common or tertiary pattern, the

score encompasses the most common pattern and worst pattern irrespective of the amount. If one site shows GS 4+5=9, 5+4=9 or 5+5=10 and the other sites have scores of 8 or less, the case would be scored as 9 or 10 for treatment purposes if the highest Gleason score is used. If the core with the highest score is only minimally involved by cancer, the overall % 4/5 could be relatively low. This contrasts with the situation where all cores are involved by GS 4+5=9, 5+4=9 or 5+5=10 tumour and the % 4/5 is 100%.

In radical prostatectomy specimens containing two grades, the % 4/5 only provides additional information in the rare situations where the Gleason scores are 3+5=8 and 5+3=8. In situations where the scores are 4+4=8, 4+5=9, 5+4=9 or 5+5=10, no useful additional information is provided since, by definition, they all have >95% patterns 4/5. However, if three patterns are present, which may each theoretically comprise 33.3% of the tumour, then the inclusion of % 4/5 would provide additional information to the Gleason score.

It is proposed that the % 4/5 measurement be performed in a similar fashion to the % pattern 4 measurement and that this be undertaken at case level. Core or specimen level reporting of % 4/5 should be considered as optional. It is suggested that the increments noted above for % pattern 4 also be used for % 4/5. In needle biopsies and radical prostatectomy specimens, the inter- and intra-observer reproducibility of % pattern 4/5 is at least as good as that of the Gleason score.[33,34] More recently, the inter-observer reproducibility of % pattern 4 on needle biopsies was found to be at a similar level, except in cases with a minimal tumour focus.[30]

Another issue worthy of consideration is whether % pattern 4 and 5 should be separately documented. Earlier studies use the combined % 4/5, while the more recent study by Sauter *et al.* separately documented the percentages of patterns 3, 4 and 5.[25,32] This latter approach provided additional prognostic information, but from a practical perspective, there are problems with borderline areas between pattern 4 and 5. Furthermore, the additional burden of work is probably beyond what should be expected from general surgical pathologists.

MINOR HIGH-GRADE (AND LOW GRADE) PATTERNS WITH TWO GRADES PRESENT

The issue of minor secondary patterns of higher grade in biopsies was first addressed at the 2005 ISUP consensus conference.[2] A minor pattern is defined as one that accounts for ≤5% of the tumour. At the consensus conference it was agreed that when a minor high-grade pattern (pattern 4 or 5) is present in a cancer with predominantly Gleason pattern 3 on needle biopsy then the high-grade pattern should be included in the score. However, if a minor low-grade pattern is present in a tumour that is predominantly high grade (pattern 4 or 5) then it should be omitted from the score. While the handling of a transurethral resection and simple prostatectomy specimens with minor high-grade patterns was not specifically addressed, the rules for biopsies are generally used.

The method of dealing with minor high grade patterns in radical prostatectomies was not specifically addressed at the 2005 conference.[2] Some pathologists follow the rules for needle biopsy and routinely include minor secondary high grade patterns in the Gleason scores, while others prefer to consider the minor secondary pattern as a 'tertiary' pattern (see next section). This means that if a tumour was 95% pattern 3 and 5% pattern 4, the former pathologists would score the tumour as GS 3+4=7 while the latter would call it GS 3+3=6 with tertiary 4.

It is proposed that when only two grades are present and one is a minor high-grade pattern, this should be recorded in all radical prostatectomy cases and may be included in the Gleason score. There is some concern that the latter option will result in significant grade inflation and the option remains to record the Gleason score as 6 (3+3) with a minor component of pattern 4. As long as the presence of a minor high grade pattern is captured, it would be easy to compare radical prostatectomy cohorts reported as GS 3+3=6 with a minor component of pattern 4 with GS 3+4=7 with ≤5% pattern 4. Importantly, pathologists should be conservative in assigning pattern 4 in cases where the tumour is predominantly pattern 3. The identification of pattern 4 should be undertaken at low power. The recognition of a few ill-defined glands or borderline gland fusion on high power should not be equated with pattern 4 (Fig. 2A,B). Likewise, pathologists should be cautious in the diagnosis of small foci of Gleason pattern 5 and not overcall tangentially cut ill-formed glands of pattern 4 (Fig. 2C,D).

When a minor low grade (≤5%) pattern is seen in a radical prostatectomy, it should be ignored. For instance, if there is ≥95% pattern 4 and <5% pattern 3, the latter should not be included in the score.

MINOR HIGH-GRADE PATTERNS WITH THREE GRADES PRESENT

It is recognised that three or more grades can be present in some prostate cancers and indeed this phenomenon was reported by Gleason in his original series.[35] The proportion of cases showing tertiary patterns ranges up to 48%; however, this varies from series to series depending on which definition of tertiary grade is used.[36] The concept of a 'tertiary' grade evolved from the work of Pan *et al.* who defined tertiary grade as a higher grade (4 and/or 5) which occupied <5% of the overall tumour.[37] Unfortunately, the term 'tertiary' was used differently by other pathologists who interpreted the word literally to mean the third pattern and hence only used 'tertiary' when three distinct patterns were present. Some investigators included both tertiary high grade and low grade patterns when three distinct patterns were present.[38,39] The usage of the term 'tertiary' when only two patterns are present is semantically incorrect. For instance, in a radical prostatectomy with 95% pattern 3 and 5% pattern 4, the term 'GS 3+3=6 with tertiary 4' is illogical. For this reason, at the 2014 consensus conference, it was agreed that the term 'minor high-grade pattern' would be used instead of 'tertiary'. This term works equally well in cases with either two or three grades present.

In needle biopsies with three grades present (patterns 3, 4 and 5), minor high-grade patterns are routinely incorporated into the Gleason score. The concept of reporting the primary pattern (i.e., the most predominant) and the worst remaining pattern was first introduced in 2000 in the College for American Pathologists prostate cancer protocol.[40] This practice was subsequently endorsed at the 2005 ISUP consensus conference.[2] In an example where a tumour is 60% pattern 4, 35% pattern 3 and <5% pattern 5, the score is reported as GS 4+5=9. The same principles can be applied for TURP and enucleation specimens.

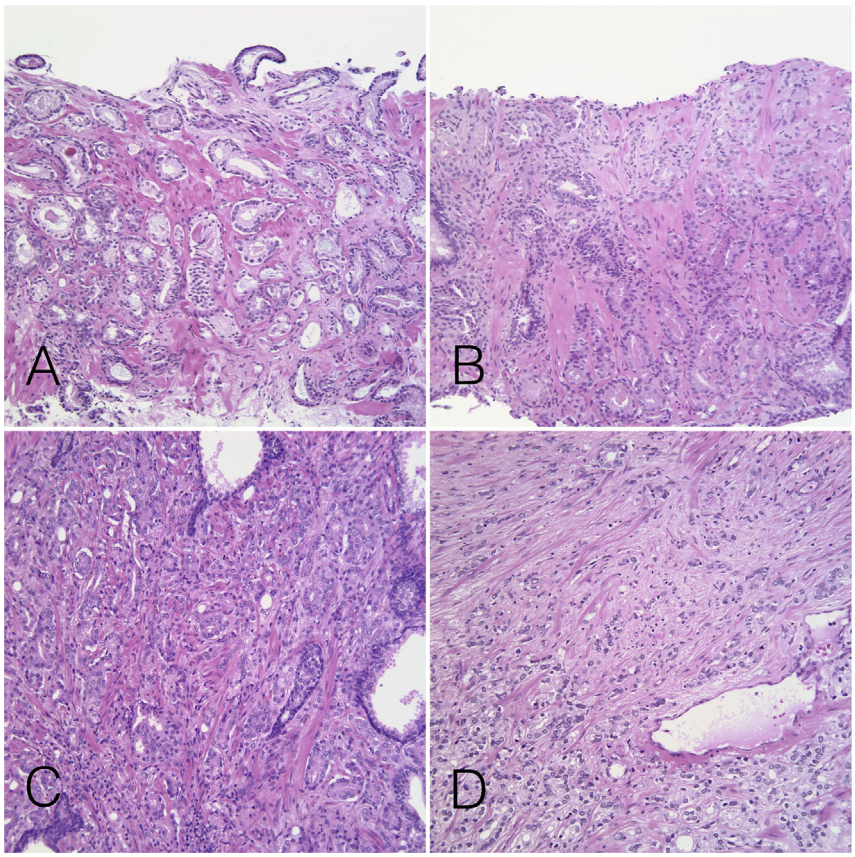

Fig. 2 (A) Gleason pattern 3 with tangential cut (small area in lower right quadrant). Needle biopsy specimen. (B) Gleason pattern with focal 4 (poorly formed glands). Needle biopsy specimen. (C) Gleason pattern 4 with tangential cut (strands of epithelium in centre). Radical prostatectomy specimen. (D) Gleason pattern 4 with focal 5 (single cells and strands in upper half of the field). Radical prostatectomy specimen.

The handling of minor high-grade patterns in radical prostatectomies is more problematic. At the 2005 ISUP meeting it was decided that tertiary patterns should be separately reported in a note, but not incorporated into the Gleason score.[2] No explicit % cut-off was mentioned for excluding a third (tertiary) pattern in the Gleason score. Subsequent reporting protocols from the College of American Pathologists and other international colleges contained a data element for tertiary pattern and suggested a cut-off of 5%.[16,18,41] While there is some direction on dealing with minor high grade patterns ($\leq$5% volume), the situation where pattern 5 was present as a third non-minor pattern, i.e., 6–33% of the overall tumour, was not addressed. In this situation some pathologists have included pattern 5 as the secondary pattern while others have continued to list it as a tertiary pattern and give some indication of the % pattern 5 in the diagnostic field or in a comment section of the report. In the WHO blue book, it has been suggested that when pattern 5 is the third most common pattern and occupies >5% of the tumour it should be incorporated in the score, although this recommendation was not specifically discussed at the WHO consensus meeting.[10] Further research needs to be undertaken before a method of handling non-minor tertiary patterns in radical prostatectomies can be fully endorsed.

There have been some recent studies suggesting that the integration of minor (so-called tertiary) patterns into ISUP grade can improve the accuracy of predicting PSA recurrence following radical prostatectomy.[42–44] However, for the time being, the presence of a minor component of pattern 5 in a Gleason score 7 case should not affect the assignment of ISUP grade.

THE LEVEL OF BIOPSY REPORTING (CORE, SPECIMEN, CASE)

There are significant variations in the number and distribution of samples from the prostate gland and how these are labelled and submitted to the laboratory. A typical prostate biopsy case consists of 10–14 cores, but some protocols provide 15 or more cores. In addition to systematic biopsies, targeted ultrasonic and magnetic resonance imaging (MRI) guided biopsies are being taken with increased frequency. For a typical 12 core systematic biopsy the sampled cores may be received in 12 separate specimen containers with site-specific labels, six containers with typical sextant designations each containing two cores, or six cores in each of two containers labelled left and right. From the technical quality perspective, single core, site-specific labelled submission and blocking is ideal, although two cores submission and blocking is acceptable.[45] If more than two cores are present in a container, there is an increased risk of fragmentation which leads to problems with the histological processing and reporting.

The ISUP has recommended that Gleason grading be undertaken at core level if the cores are separately identified.[1,2] This approach has been endorsed by the WHO.[10] This recommendation is easily followed for single core, site-specific labelled specimens or for cases in which multiple

cores are labelled with different inks indicating their location, but submitted in one specimen container. However, when multiple unidentified cores are submitted in a single specimen container and multiple cores contain cancer, the pathologist may choose to report aggregated Gleason score and tumour extent measurements for the entire specimen. Therefore, the minimum reporting requirement is at the specimen (container, jar, pot) level with more detailed reporting of individual cores being considered optional (Table 2, Fig. 3). In this situation, workload implications need to be considered. Most workload measurement systems use the specimen as the unit of work and not individual pieces or fragments that constitute a single specimen. The best way for the urologist to ensure that reporting is at core level is to provide individual labelled cores.

Case level reporting of prostate biopsy parameters, while considered optional by many, is of great value to the urologist or oncologist, especially when there are multiple cores (specimens) involved by tumour.[15,17,27] In case level reporting, the Gleason score and other Gleason derivatives, including ISUP grade and % patterns 4 and 5 or % pattern 4/5 measurements are captured. This allows the clinician to view all relevant information in one field of their report rather than try to determine the Gleason score for treatment purposes, as well as other measurements, by viewing individual core/specimen diagnostic lines. The case level synopsis is also of value when discussing results with patients and in assembling data for use in nomograms. With respect to grading, the following parameters should be included in a case level report: Gleason score (including primary and worst remaining pattern) and the ISUP grade. For Gleason 7 cases, a % pattern 4 measurement should be recorded (see previous section). For Gleason scores 8 and above, % 4/5 or % 4 and % 5 individually may also be provided. In general, the highest Gleason score is the one to be recorded in the case level summary; however, in situations where there is grading diversity across individual core/specimens and the highest Gleason score is minor in extent, a composite Gleason score may also be reported (see later discussion). Furthermore, in cases where there is a mixture of systematic and MRI targeted biopsies, the Gleason score of the positive targeted biopsies may be separately recorded in the case summary.

It is proposed that when a case level summary, which includes a Gleason score and derivative measurements, is used, it is not necessary to record the derivative measurements including ISUP grade, and % patterns 4 and 5 or 4/5 at individual core/specimen level. A simple diagnostic line to include the diagnosis, Gleason score (primary, worst remaining) and relevant extent measures would suffice. However, if a case level report is not utilised, Gleason score and all relevant derivative measurements should be included at the core/specimen level. It should be noted that the amount of information provided on a per core basis can be overwhelming, with more than 10 discrete data components (Gleason score, primary grade, worst remaining grade, ISUP grade, % pattern 4 and 5 or % pattern 4/5, number of positive cores, total cores, percent tissue involvement, linear millimetres of tissue involvement, perineural invasion, periprostatic fat invasion). In the case of 12 positive biopsies, the amount of information for clinicians to assimilate can be staggering, especially when there is inter-site grade diversity. A case level report helps to synthesise and thus simplify the recording of relevant prognostic factors for clinical usage.

DIVERSITY IN GLEASON SCORES AMONG CORES (HIGHEST VERSUS COMPOSITE GRADE)

In biopsy cases, it is not uncommon for cores to have different Gleason scores. When the cores are submitted in a fashion that allows their separate identification, the urologist or oncologist may be faced with three or more separate scores from which to choose the score for treatment purposes. At the 2014 consensus meeting, it was reported that the majority of clinicians present at the meeting used the highest (worst) score for treatment planning and prognostication. While this approach is the norm in North America, in Europe and elsewhere it is common for pathologists to report a global (overall, composite) Gleason score for a biopsy case.[29,46] This observation has been reinforced in a recent survey of European uropathologists, where it was reported that 77% of participants calculated a global score.[46]

The arguments in favour of taking the highest Gleason score as the score for the case are anchored in the belief by many clinicians that prostate cancer is multifocal and that its behaviour is determined by the highest-grade element, akin to other genitourinary tumours such as urothelial malignancy and renal cell carcinoma. However, this belief is completely contrary to the fundamental principle of the Gleason system, i.e., that the behaviour of prostatic adenocarcinoma is based on the relative proportions of various histological patterns and not solely on the worst pattern. Some studies have shown that the highest score in a core better correlates with radical prostatectomy stage and Gleason score than the average or most prevalent score among cores.[47,48] In other studies, the overall Gleason score performed in a similar fashion or better than worst Gleason score, when biochemical recurrence or cancer death rates were used as endpoints.[49,50] It is interesting to note that many risk calculators including the Partin tables, were constructed and validated using the highest Gleason score.[51]

Table 2 Needle biopsies: reporting levels for Gleason score and derivatives

Level of reporting	Parameters			
	Gleason score	ISUP grade	% pattern 4 (Gleason 7)	% patterns 4 and 5 or 4/5 (Gleason 8–10)
Core (separately identified)	Recommended	Optional if reported at case level	Optional if reported at case level	Optional if reported at case level
Specimen	Recommended	Optional if reported at case level	Optional if reported at case level	Optional if reported at case level
Case[a]	Recommended	Recommended	Recommended	Recommended

[a] Case level reporting is optional but when used it should include listed parameters.

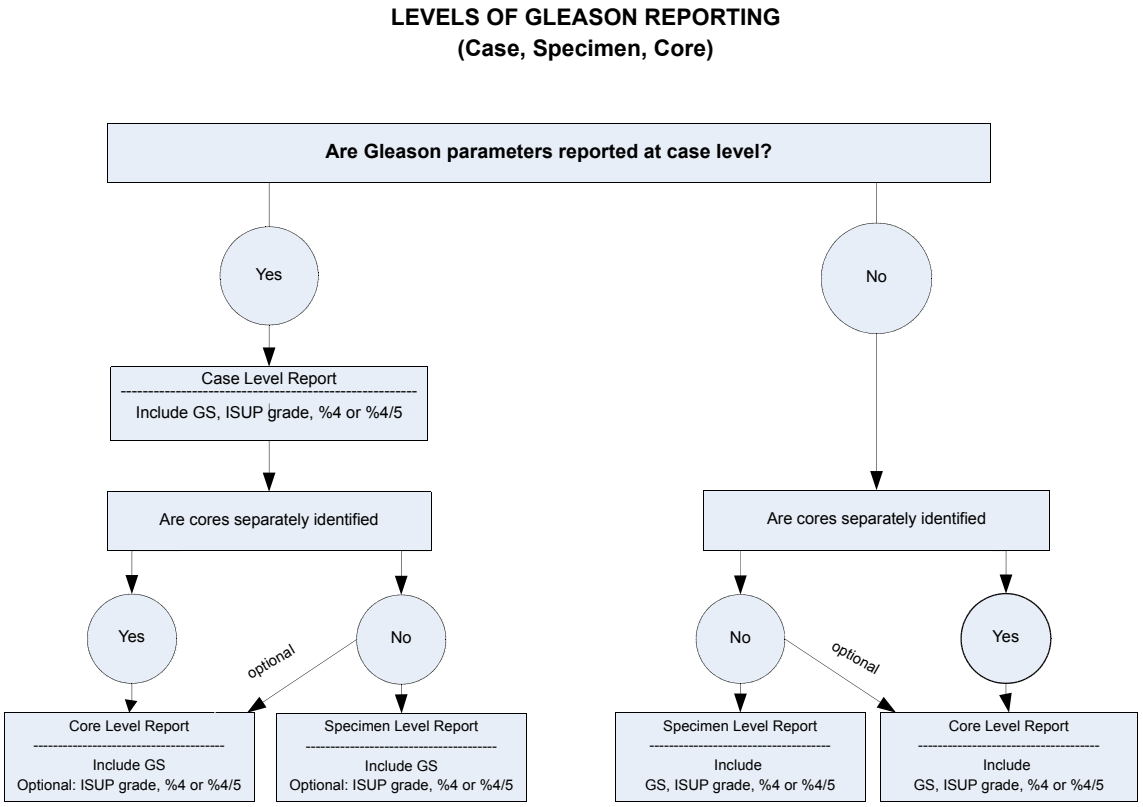

Fig. 3 Algorithm for reporting Gleason score (GS), ISUP grade and derivative measurements at case, specimen and core level.

The practice of using the highest Gleason score has undoubtedly contributed to the recent trend of Gleason grade inflation[52] and it can also lead to significant downgrading at the time of radical prostatectomy.[47,53] In individual patients, the reporting of highest Gleason score (without qualification in a comment) can be misleading. They would likely be classified as high risk and be subject to additional imaging and more aggressive treatment options compared to those with intermediate risk disease.[54]

In the scenario where multiple sites were involved by Gleason score 3+4=7 and one site showed a small focus of Gleason score 4+4=8 (Fig. 4), a slim, but not consensus level majority (51%) of attendees at the 2014 consensus conference considered Gleason 3+4=7 as the score for treatment purposes, even though one core contained low volume Gleason score 8 cancer. When asked about the most likely score at radical prostatectomy, 75% responded with GS 3+4=7. In situations where there is grade diversity among cores, it may be worthwhile to provide a composite Gleason score in a comment or case level synopsis.

GRADING OF SEPARATE TUMOUR FOCI IN RADICAL PROSTATECTOMY SPECIMENS

One of the unique features of acinar adenocarcinoma of the prostate is its remarkable multifocality. It has been reported that up to 88% of these cancers have more than one tumour focus.[55,56] In only 9% of the patients, all foci were of the same Gleason score.[55] This adds to the challenges of grading prostate cancer.

At the 2009 ISUP Consensus Conference on Handling and Reporting of Radical Prostatectomy Specimens, it was recommended that the dominant tumour nodule(s) of multifocal cancer be graded separately.[57] The rationale for this is the assumption that an additional low-grade tumour does not improve the prognosis of a tumour of higher grade. For example, if a peripheral zone cancer is GS 4+4=8 and a separate transition zone cancer is GS 3+3=6, then including all cancer in a single score would result in a global GS of 3+4=7 or 4+3=7, depending on the size of the nodules. Such

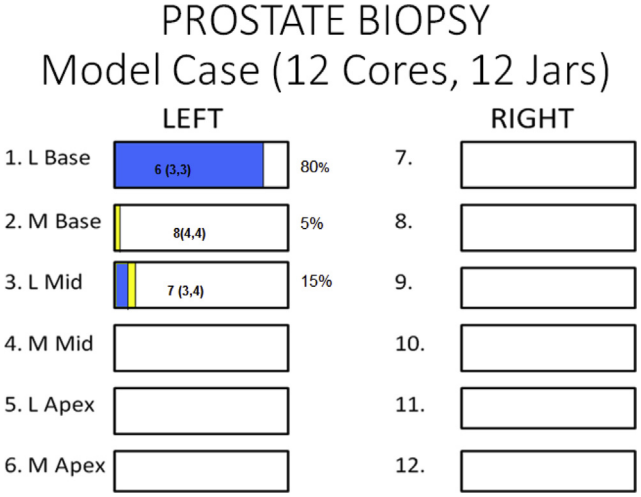

Fig. 4 Schematic showing situation where three biopsies from contiguous sites show grade diversity. A small focus of Gleason score 4+4=8 is noted in the left medial base site while left lateral base site shows abundant Gleason score 3+3=6. The lateral mid site contains a small amount of Gleason score 3+4=7 tumour. The composite Gleason score in this situation would be 3+4 =7 with less than 10% pattern 4. If the highest Gleason score is used for treatment purposes, the patient would be classified as high risk (Gleason 8–10). If this patient underwent radical prostatectomy, the Gleason score would likely be 3+4=7.

a grade dilution of the GS may not accurately reflect the outcome. However, there are several problems with this approach. First of all, there is disagreement as to the definition of dominant tumour or index tumour as defined at the 2009 ISUP conference.[57] In most cases the largest focus also has the highest grade but occasionally a small tumour has a higher grade than a much larger, low-grade tumour. In one study, a discordance between highest GS, largest tumour volume and extraprostatic extension was noted in 11.3% of multifocal cancers on radical prostatectomy.[56] A very large low-grade tumour may be more important prognostically than a minimal tumour of higher grade, but it is impossible to be sure of this in the individual patient. A similar situation occurs when a tumour of lower grade has extra-prostatic extension while a high-grade tumour focus is organ-confined.

The growth pattern of prostate cancer is highly infiltrating and branching. It may be difficult to determine if tumour areas are from separate foci or parts of the same tumour nodule. When a radical prostatectomy specimen is partially embedded as practised in some laboratories, it is very difficult, if not impossible, to determine if the tumour is multifocal. Whole mount sections of horizontal slices of entire prostatectomy specimens greatly facilitate the reconstruction of the three-dimensional structure of the tumour (or tumours). However, not all laboratories have sufficient resources for whole mounting and this technique also has certain technical disadvantages relating to transportation of slides, re-cutting for immunohistochemical evaluation and archiving of slides.[58]

The remarkable morphological heterogeneity of prostate cancer is paralleled by a genetic heterogeneity. It has been shown that spatially separated tumour foci are somatically independent,[59] but there is also a pronounced intra-tumoural genetic heterogeneity.[60] When tumour foci enlarge, they will ultimately merge into what seems to be one single focus. Intra-tumoural morphological heterogeneity may suggest that separate foci have merged but given the inherent heterogeneity of prostate cancer it is indeed difficult to be certain of it. Occasionally the findings may be quite compelling for merging of foci, e.g., when there is one tumour component in the peripheral zone and an adjacent component in the transition zone with contrasting grade and morphology.

The notion that the tumour of the highest grade must be most important for the patient has been challenged in recent genetic analyses. In one study, whole-genome sequencing was used for tracking of the metastatic cancer clone of a single case. Unexpectedly the lethal clone came from a small, low-grade focus and not from a large higher-grade primary cancer.[61] Similarly, genetic mapping of a single case of prostate cancer with lymph node metastases revealed that the metastases were not derived from invasive Gleason score 9 cancer but from a component of intra-ductal prostatic adenocarcinoma.[60] Thus, it may not be possible to identify morphologically the clinically most important tumour clone. Until there is evidence-based guidance as to how multifocal and heterogeneous prostate cancer should be reported, it is suggested that the tumour foci with the highest grades, volumes and stages are reported separately. The importance of total embedding of radical prostatectomy specimens should be emphasised, as this greatly facilitates the mapping of the spatial distribution of separate foci.[62]

SUMMARY AND RECOMMENDATIONS

The proposed recommendations for grading prostate cancer (Table 3) deal with practical aspects of applying the Gleason system in modern day practice. While some of these recommendations have been endorsed at the 2014 ISUP consensus conference, many items were not fully discussed or polled at the meeting. There is not a strong evidence base for many of these guidelines. The proposed recommendations mostly reflect expert opinion and they are classified as established if there has been prior agreement by consensus and provisional if there was no previous agreement or if the item was not discussed at prior consensus conferences. Future research and consensus activities will hopefully address some

Table 3 Summary of Established and Provisional Recommendations

Established and Provisional Recommendations
• Report Gleason score and ISUP grade in each positive case (E)
• Report Gleason score for every separately identified positive core (E)
• Report overall Gleason score when non-identified cores are aggregated in one specimen container; individual core reporting is optional (E)
• When case level report is used, Gleason score, ISUP grade and derivative measurements should be included in the summary; the Gleason score should also be included at the core/specimen level (P)
• When case level report is not used, Gleason score, ISUP and derivative Gleason measurements should be included at the core/specimen level (E)
• For Gleason score 7 cases (ISUP grade 2 or 3) report % pattern 4 (E) o Required for ISUP grade 2 and recommended for ISUP grade 3 (P)
• % pattern 4 should be quantified as follows: ($\leq$5%, 6–10% and subsequent 10% increments) (P)
• For small foci of Gleason 7 ($\leq$3 mm), % pattern 4 is considered optional (P)
• For Gleason scores 8–10 (ISUP grades 4,5), reporting % 4 and % 5 or % 4/5 is considered optional but may be of value, especially in cases showing grade heterogeneity (P)
• Minor low-grade patterns should not be included in the Gleason score in needle biopsy specimens (E) and other specimen types (P)
• Minor high-grade patterns should be included in the Gleason score when two patterns are seen in needle biopsy, TUR/SP specimens (E)
• Minor high-grade patterns should be recorded when 2 patterns are seen in RP specimens and may be included in the Gleason score (P)
• A minor high-grade pattern should be included in the Gleason score when 3 grades are present in NB, TUR/SP specimens (E)
• When three grades are present in a RP and pattern 5 is $\leq$5%, it should not be included in the Gleason score; the % pattern 5 should be recorded separately (E)
• When 3 grades are present in a RP and pattern 5 is 6–33%, it may be included in the Gleason score; the % pattern 5 should also be recorded separately (P)
• When there is grade diversity across sites, a composite Gleason score may be generated which should be included in the case level report or in a comment (P)
• In RP specimens with multifocal adenocarcinoma, Gleason score and derivative measurements should be given for the dominant tumour nodule(s) (E)
• In RP specimens with diffuse or multifocal adenocarcinoma where a dominant nodule is not clearly identified, the Gleason score and derivatives should be based on all identified tumour (P)

(E), Established recommendation through prior consensus activities; (P), provisional recommendation: further research and consensus required. NB, needle biopsy; RP, radical prostatectomy; TUR/SP, transurethral resection/simple prostatectomy.

of the deficiencies, for instance in the handling of tertiary patterns in radical prostatectomy cases. However, for the time being the proposed recommendation framework is pragmatic and will help ensure some uniformity of approach moving forward. The proposed recommendations also allow some flexibility in reporting which reflects the variation in urological pathology practice internationally.

Conflicts of interest and sources of funding: The authors state that there are no conflicts of interest to disclose.

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